KCC 4749.1
K-C 16,858.1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Rae Ellen Syverson, et al. Art Unit 1615
Serial No. 10/803,819
Filed March 18, 2004
Confirmation No. 7018
For INHIBITION OF EXOPROTEIN PRODUCTION USING AROMATIC COMPOSITIONS IN NON-ABSORBENT ARTICLES
Examiner Lakshmi Sarada Channavajjala

March 19, 2007

APPEAL BRIEF

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

REFERENCES

CASES

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APPEAL BRIEF

This is an appeal from the final rejection of the claims of the above-identified application made in the Office action dated November 30, 2006. A Notice of Appeal was filed on January 17, 2007.

I. REAL PARTY IN INTEREST

The real party in interest in connection with the present appeal is Kimberly-Clark Worldwide, Inc. of 401 N. Lake Street, Neenah, Wisconsin 54957-0349, a corporation of the state of Delaware, owner of a 100 percent interest in the pending application.

II. RELATED APPEALS AND INTERFERENCES

Appellants are aware of one pending appeal, which may be related to, directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal. Specifically, a Notice of Appeal was filed in U.S. Application No. 09/969,299 on December 29, 2005, an Appeal Brief was filed

in this case on February 27, 2006, and a substitute Appeal Brief was filed in this case on November 9, 2006.

III. STATUS OF CLAIMS

Claims 1-60 are currently pending in the application, and claims 5, 12, 13, and 26-60 have been withdrawn. A copy of the pending claims appears in the Claims Appendix of this Brief.

Claims 1-4, 6-11, and 14-25 stand rejected under 35 U.S.C. §103(a). The rejection of claims 1-4, 6-11, and 14-25 under 35 U.S.C. §103(a) is being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been filed after the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary correlates claim elements to specific embodiments described in the application specification, but does not in any manner limit claim interpretation. Rather, the following summary is provided only to facilitate the Board's understanding of the subject matter of this appeal.

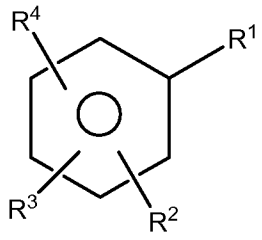
Certain bacterial proteins and metabolic products produced by vaginal bacteria can have a beneficial effect on other microorganisms and the human host, such as providing protection and resistance to infection and making the vagina inhospitable to some species of bacteria such as, for example, *Staphylococcus aureus* (*S. aureus*) (see Specification at p. 2, ¶5). Other microbial products found in the vagina may negatively affect the human host. For example, *S. aureus* can produce and excrete into

its environment a variety of exoproteins including enterotoxins, Toxic Shock Syndrome Toxin-1 (TSST-1), and enzymes such as protease and lipase. When absorbed into the blood stream, TSST-1 produces toxic shock syndrome (TSS) in non-immune humans (see Specification at ¶6)

When *S. aureus* is present in an area of the human body that harbors a normal microbial population such as the vagina, it may be difficult to eradicate the *S. aureus* bacteria without harming members of the normal microbial flora required for a healthy vagina. Typically, antibiotics that kill *S. aureus* are not an option for use in catamenial products because of their effect on the normal vaginal microbial flora and their propensity to stimulate toxin production if all of the *S. aureus* are not killed (see Specification at ¶10).

There is thus a need for compounds that will effectively inhibit the production of TSST-1 from Gram positive bacteria, and be substantially non-harmful to the natural flora found in the vaginal area (see Specification at ¶12).

Independent claim 1 of the present application is directed to an exoprotein inhibitor for inhibiting the production of exoproteins from Gram positive bacteria in and around the vagina (see Specification, ¶15) comprising a non-absorbent substrate for insertion into a vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche (see Specification ¶14 and 15), the non-absorbent substrate having deposited thereon an effective amount of a first active ingredient having the general formula:



wherein R^1 is $-OR^6OH$ (see Specification ¶21); R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety (see Specification ¶21); R^2, R^3, and R^4 are independently selected from the group consisting of H, OH, COOH, and $-C(O)R^9$ (see Specification ¶21); R^9 is hydrogen or a monovalent saturated or unsaturated aliphatic hydrocarbyl moiety (see Specification ¶21), wherein the first active ingredient is effective in inhibiting the production of exoprotein from Gram positive bacteria (see Specification ¶21 and 24). (See also claim 1 as originally filed).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-4 and 6-10 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Stolar, et al. (U.S. Patent No. 4,470,978) in view of D'Augustine, et al. (U.S. Patent No. 6,416,779), and claims 14-25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Stolar, et al. (U.S. Patent No. 4,470,978) in view of D'Augustine, et al. (U.S. Patent No. 6,416,779) and Syverson (U.S. Patent No. 5,612,045).

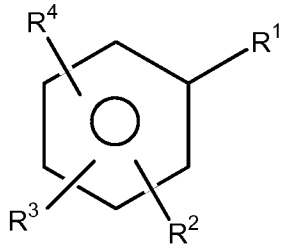
The Examiner has also indicated in the Office Action Summary that claim 11 is rejected, but has failed to set forth any specific grounds of rejection in the Office action.

Applicants therefore submit that claim 11 should also be allowed.

VII. ARGUMENT

Claims 1-4 and 6-10 are patentable under 35 U.S.C. §103(a) over Stolar (U.S. Patent No. 4,470,978) in view of D'Augustine, et al. (U.S. Patent No. 6,416,779)

Independent claim 1 is directed to an exoprotein inhibitor for inhibiting the production of exoproteins from Gram positive bacteria in and around a vagina. The exoprotein inhibitor comprises a non-absorbent substrate for insertion into the vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche. The non-absorbent substrate has deposited thereon an effective amount of a first active ingredient having the general formula:



wherein R^1 is $-OR^6OH$; R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety; R^2, R^3, and R^4 are independently selected from the group consisting of H, OH, COOH, and $-C(O)R^9$; R^9 is hydrogen or a monovalent saturated or unsaturated aliphatic hydrocarbyl moiety, wherein the first active ingredient is effective in inhibiting the production of exoprotein from Gram positive bacteria.

Stolar discloses an antibacterial pharmaceutical composition to treat bacterial infections comprising effective amounts of a combination of phenoxyethanol, trimethoprim, and an antibacterial sulfa drug. The composition is for internal administration, and can be distributed in a pharmaceutically acceptable carrier. Examples of suitable carriers include sugar, dextrin, dextrose, sodium chloride, and the like.[1]

Stolar fails to disclose a non-absorbent substrate for insertion into the vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche. In an attempt to find each and every element of claim 1 as required by the M.P.E.P. for a determination of *prima facie* obviousness, the Office cites the D'Augustine et al. reference for combination with Stolar.

D' Augustine et al. disclose devices, methods, and compositions for treating vaginal fungal, bacterial, viral, and parasitic infections by intravaginal or transvaginal administration of therapeutic and/or palliative antifungal, antibacterial, antiviral or parasiticidal drugs to the vagina or to the uterus. Specifically, a device such as a tampon, tampon-like device, vaginal ring, pessary, cervical cup, vaginal sponge, intravaginal tablet, or intravaginal suppository, delivers the drug, which can be in the form of a paste, cream, ointment, microcapsule, solution, powder, or gel having a sufficient thickness to maintain prolonged vaginal epithelium and mucosa contact. In one embodiment, the drug can be

[1] Applicants note that, as discussed in more detail below, Stolar does not disclose phenoxyethanol as an antibacterial agent; he only describes phenoxyethanol as a single component of a three-

incorporated into a cream, lotion, foam, paste, ointment, or gel which can be applied to the vagina using an applicator.[2]

The Examiner asserts in the Office action that, as Stolar teaches phenoxyethanol as an effective antimicrobial agent and D'Augustine, et al. disclose effective delivery of antimicrobial compounds through vaginal devices to vaginal mucosa and vaginal epithelium, it would have been obvious for one skilled in the art at the time of the instant invention to add the phenoxyethanol of Stolar to the non-absorbent feminine devices of D'Augustine, et al. for treating microbial or bacterial infections in the vaginal area of females. Applicants respectfully disagree, and submit that the Examiner is misinterpreting the Stolar reference.

The Examiner has stated that since Stolar suggests including a synergistically effective amount of phenyxoethanol in the "antibacterial composition," this implies that phenoxyethanol has antibacterial properties. However, as noted above, Stolar does not disclose phenoxyethanol as an antibacterial agent. Rather, phenoxyethanol is described merely as a single component of a three-component composition, wherein the composition has antibacterial properties. There is, however, no disclosure that phenoxyethanol alone has any antibacterial properties, much less that phenoxyethanol is effective in inhibiting the production of exoprotein from Gram positive bacteria.

Rather, Stolar merely discloses that when added to a composition comprising a sulfa drug and trimethoprim, phenoxyethanol synergistically increases the antibacterial

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component antibacterial composition. Stolar fails to disclose that phenoxyethanol alone has antibacterial properties.

[2] D' Augustine et al. at column 18, lines 24-26.

activity of the composition. This disclosure, however, is not a suggestion or teaching as to the antibacterial effect of phenoxyethanol in the absence of trimethoprim and a sulfa drug. In fact, Stolar explicitly teaches that phenoxyethanol will not act synergistically with just any combination of drugs, but rather states only that the synergistic effect occurs when phenoxyethanol is combined with a sulfa drug and trimethoprim. For instance, Stolar states at column 1, lines 58-61 that synergistic activity is not observed when phenoxyethanol is added to either the sulfa drug alone or the trimethoprim alone.[3]

Furthermore, Stolar actually teaches that phenoxyethanol is not an effective antibacterial (for internal administration) when administered in the absence of a sulfa drug and trimethoprim. For instance, in Example 6, Stolar evaluates the effectiveness of compositions comprising a combination of a sulfa drug, trimethoprim, and phenoxyethanol, compositions comprising two of the three drugs, or compositions comprising only a sulfa drug, trimethoprim, or phenoxyethanol when the compositions are administered orally to chicks.[4] The results show that of the eight chicks administered phenoxyethanol alone, none were cured, and seven of the eight were either sick or

[3] "It has surprisingly been found that when phenoxyethanol is added to a mixture of a sulfa drug and trimethoprim that the synergistic activity of the overall composition is increased to an unexpected extent. This is most surprising in view of the fact that when phenoxyethanol is added to either the sulfa drug alone or the trimethoprim alone, no such activity is observed." Stolar at col. 1, ln. 55-61.

[4] In Example 6 of Stolar, chicks were given 300 ml of water containing one of the compositions, and on the following day were given an injection of 0.5 ml suspension of 2 x 10^6 organisms of E. coli in 5% mucin solution. The chicks were also given another treatment of the medication. The treatment was continued for 2 more days post infection. The severity and presence or lack of infection in each chick was recorded as of the 11th day post inoculation. The chicks were categorized as either "cured," "slightly sick," "sick," or "dead," with "cured" and "slightly sick" being considered as one group and "sick" and "dead" being considered as another group. Stolar at col. 4, ln. 30 to col. 5, ln. 3.

died.

In light of the foregoing, applicants submit that there is no reason based on the disclosure of Stolar for one skilled in the art to specifically select phenoxyethanol to incorporate into the devices of D'Augustine, et al. to treat microbial or bacterial infections in the vaginal area. In particular, why would one skilled in the art pick phenoxyethanol from the three-drug cocktail disclosed in Stolar to incorporate into the devices of D'Augustine, given the teaching in Stolar that phenoxyethanol is not an effective antimicrobial when used in the absence of the sulfa drug and trimethoprim? One skilled in the art could not and would not be so motivated.

Nor would one skilled in the art be motivated to incorporate the three drug compositions of Stolar into a non-absorbent substrate for insertion into a vagina. As noted above, the Stolar reference is directed to antibacterial compositions suitable for administration, particularly oral administration, to treat bacterial infections in humans and animals. For example, as noted above, in Example 6 chicks were orally treated for *Eschericia coli* (*E. coli*) infection by mixing the Stolar antibacterial composition with the chicks' drinking water. As such, why would one skilled in the art look to the Stolar antibacterial, orally-administered composition over any other antibacterial compositions for use in the intravaginal devices of D' Augustine et al.? Nowhere in Stolar is it disclosed to use the antibacterial composition for the treatment of vaginal fungal, bacterial, viral, and parasitic infections.

Furthermore, the disclosure in Stolar of routes of administration other than tablets does not amount to motivation

to incorporate the compositions of Stolar into a non-absorbent substrate for insertion into a vagina.[5] As mentioned in applicants' specification and shown in the examples, the first active ingredient used in the exoprotein inhibitor of claim 1 of the present invention is not acting as an antimicrobial agent as apparently understood by the Examiner. As mentioned in Applicants' specification, the first active ingredient acts to inhibit the production of exoproteins from Gram positive bacteria, but does not seek to kill the bacteria as the killing of bacteria is non-selective and the "good" bacteria needed to maintain a healthy vagina would also be killed. Thus, the non-selective killing of bacteria could actually be very harmful to the vagina and could cause serious health problems. This is significant. The first active ingredient as claimed in claim 1 of the present invention actually seeks not to act as an antimicrobial agent as claimed by the Examiner, but seeks to only prevent the production of potentially harmful by-products of bacteria, while allowing the bacteria to live. It is also noted that none of the cited references suggest or disclose that a composition having the general formula of the first active ingredient of claim 1 can act in such a manner. Since not all antimicrobial agents are suitable for use in a vagina, in the absence of any teaching or suggestion that phenoxyethanol alone or the compositions of Stolar in general are suitable for use in a vaginal environment, the mere disclosure in Stolar of routes of administration such as solutions and suppositories does not amount to a teaching or suggestion to use phenoxyethanol alone or the three drug Stolar composition in a vaginal environment.

[5] The Examiner states that Stolar teaches solutions and suppositories as well as tablets, thus suggesting other routes of administration, rendering moot

Additionally, even assuming that phenoxyethanol is disclosed as an antibacterial as suggested by the Examiner (which, as discussed above, applicants disagree with), why would one skilled in the art pick Stolar's composition of sulfa drug, trimethoprim, and phenoxyethanol over all of the other non-toxic, antibacterial compositions present in the art, particularly when D'Augustine et al. provide numerous suitable antibacterial compositions to use with their devices, and provide no suggestion that compounds having the structure set forth in applicants' claim 1 would be suitable alternatives? D' Augustine et al. simply teach compositions that can be used as antibacterials to treat bacterial infections of the vagina and devices for delivering the compositions; and even provide several commercially acceptable antibacterial compositions. The D' Augustine et al. reference fails to provide a reason why one skilled in the art would choose another antibacterial over those listed in the D' Augustine et al. reference or disclosed elsewhere in the art, and fails to suggest that phenoxyethanol or the compositions of Stolar, in general, could or should be used in the vagina. Nor does Stolar provide such motivation since, as discussed above, there is no disclosure or suggestion in Stolar to use the antibacterial composition for the treatment of vaginal fungal, bacterial, viral, and parasitic infections.

In this regard, applicants further note that sulfa drugs are well known broad spectrum antimicrobial drugs. However, for the reasons discussed above, administration of such broad spectrum antimicrobial drugs to the vaginal area may actually harm beneficial vaginal flora, thus upsetting the balance of flora in the vagina. Consequently, if anything, one skilled in

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the idea that an oral composition cannot be combined with non-absorbent devices.

the art would be motivated not to incorporate the compositions of Stolar into the vaginal devices of D'Augustine, et al.

Furthermore, the D'Augustine et al. reference is directed to treating infections such as *Haemophilus vaginitus* and *Corenebacterium vaginitis* caused by anaerobic bacteria such as *Gardnerella vaginalis* or *Mycoplasma huminus*. No where in the D'Augustine et al. reference are infections caused by *Eschericia coli* taught or suggested. As such, one skilled in the art would not, and could not, be motivated to use the antibacterial three-drug composition of Stolar, which, as shown in the working Examples is effective against *Eschericia coli*, over the antibacterials discussed in the D'Augustine et al. reference directed to treating the infections caused by *Gardnerella vaginalis* or *Mycoplasma huminus*.

With all due respect, it appears that the Office has used impermissible hindsight analysis and reconstruction when combining the Stolar and D' Augustine et al. references to arrive at Applicants' claim 1.[6] Notably, it would be clear to one skilled in the art reading D' Augustine et al. that an antibacterial composition could be used to treat bacterial vaginal infections. There are, however, a myriad of antibacterial compositions, many of which are used to treat vaginal infections. What is important is that there is no motivation or suggestion to use 1) phenoxyethanol in the absence of sulfa drugs and trimethoprim as disclosed in Stolar, or 2)

[6] *Grain Processing Corp. v. American-Maize-Products, Co.*, 840 F.2d 902, 904 (Fed. Cir. 1988). M.P.E.P. §2142 provides that in order to reach a proper determination under 35 U.S.C. §103(a), the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. Knowledge of Applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences." The tendency to resort to "hindsight" based upon Applicant's disclosure is often difficult to avoid due to the very nature of the examination process.

the three drug antimicrobial compositions of Stolar, in general, over any of the other enormous number of antibacterial compositions described in the art, which are suitable for use in a vagina, in the absence of any teaching or suggestion in either of the cited reference that phenoxyethanol could or should be used in the vaginal area.

As there is no motivation or suggestion to combine the Stolar and D' Augustine et al. references to arrive at each and every limitation of claim 1, claim 1 is patentable over Stolar in view of D'Augustine et al.

Additionally, the Examiner has made several statements responding to applicants' arguments.

In particular, in response to applicants' arguments that Stolar does not disclose phenoxyethanol as an antibacterial agent and only teaches phenoxyethanol in a group of three compounds, the Examiner has stated that Stolar clearly suggests including a synergistically effective amount of phenoxyethanol in the total "antibacterial composition", thus implying antibacterial property of phenoxyethanol.

In response, applicants submit that the mere disclosure in Stolar of an antibacterial composition comprising phenoxyethanol is not tantamount to a disclosure that phenoxyethanol has antibacterial properties and is suitable for vaginal use. In this regard, applicants note that one skilled in the art would not assume that every component of an antibacterial composition will itself necessarily have antibacterial properties simply because it is part of an antibacterial composition. This is particularly true in the case of the phenoxyethanol disclosed in Stolar. For the reasons set forth above, Stolar in fact teaches that phenoxyethanol alone or in combination with only sulfa drug or only trimethoprim will not synergistically increase the

antibacterial properties of the composition. There is simply nothing in Stolar to suggest that pheonxyethanol has antibacterial properties in the absence of sulfa drug and trimepthprim, or that phenoxyethanol should or could be used in the vaginal area, much less that phenoxyethanol can be used to inhibit the production of exoprotein from Gram positive bacteria.

As mentioned above, the Examiner has also stated that the disclosure in Stolar of tablets, solutions, and suppositories suggests routes of administration other than an oral composition, and therefore the argument that an oral composition cannot be combined with non-absorbent devices such as tampons[7] is moot.

However, as discussed above, the disclosure in Stolar of routes of administration other than tablets does not amount to motivation to incorporate phenoxyethanol or the sulfa drug, phenoxyethanol, and trimethoprim containing compositions of Stolar into a non-absorbent substrate for insertion into a vagina. Specifically, even if one skilled in the art were motivate to formulate the Stolar compositions into a tablet, capsule, ampule, suppository, suspension, or solution, as disclosed in Stolar, there is still nothing to suggest that such a composition could or should be vaginally administered. As noted above, not all antimicrobial agents are suitable for use in a vagina. Thus, in the absence of any teaching or suggestion that phenoxyethanol alone or the three drug compositions of Stolar are suitable for use in a vaginal environment, the mere disclosure in Stolar of routes of administration such as solutions and suppositories does not amount to a teaching or

[7] Applicants respectfully submit that tampons are not non-absorbent devices, as stated by the Examiner.

suggestion to use phenoxyethanol alone or the three drug Stolar compositions in a vaginal environment.

With regard to applicants' arguments that one skilled in the art would not be motivated to pick phenoxyethanol from the mixture of three compounds disclosed in Stolar for combination with the devices of D'Augustine, et al., the Examiner has stated that these arguments are not persuasive because Stolar suggests a synergistic increase in the antibacterial activity by the addition of phenoxyethanol with the other two compounds. For the reasons set forth above, applicants again note that Stolar not only fails to teach or suggest that phenoxyethanol alone has antibacterial properties, but in fact states that the synergistic effect is seen only when phenoxyethanol is used in combination with sulfa drugs and trimethoprim. Additionally, applicants note that Stolar in fact states that an object of the invention is to improve the antibacterial activity for sulfa drugs and trimethoprim.[8] This is accomplished by incorporating phenoxyethanol into a composition comprising sulfa drugs and trimethoprim. There is, however, no statement that the combination of sulfa drugs, trimethoprim, and phenoxyethanol improves the antibacterial activity of phenoxyethanol. There is simply no suggestion in either Stolar or D'Augustine, et al. that phenoxyethanol would be an effective antibacterial when used alone.

With regard to applicants' remarks as to inhibiting the production of exoprotein from Gram positive bacteria, the examiner has stated that the instant claims do not exclude killing of the bacteria along with inhibiting protein, nor do they recite that "good" bacteria is not killed. The examiner

[8] Stolar at col. 1, lines 30-32.

goes on to state that while the ultimate effect of an antibacterial agent is killing the bacteria, such an effect includes inhibiting proteins, including exoprotein, and thus the antibacterial teaching of Stolar is inclusive of inhibiting exoprotein.

In response, applicants again note that Stolar does not suggest that phenoxyethanol alone has antibacterial effects. Furthermore, applicants respectfully submit that one skilled in the art would understand that "good" bacteria present in the vagina play a beneficial role in providing protection and resistance to infection and, therefore, it is desirable that the natural flora found in the vaginal area not be substantially altered, such as by use of a broad spectrum antimicrobial.[9] As discussed above, sulfa drugs, such as are present in the compositions of Stolar, are well known broad spectrum antibacterial drugs. As such, one skilled in the art simply would not be motivated to incorporate a composition comprising sulfa drugs onto a device for use in the vagina.

Claim 1 is thus patentable over the combination of Stolar and D'Augustine, et al. Claims 2-4 and 6-10 depend directly or indirectly on claim 1. As such, claims 2-4 and 6-10 are patentable for the same reasons as claim 1 set forth above, as well as for the additional elements they require.

Claims 7-9

Additionally, claims 7-9, which depend from claim 1, further set forth the amount of first active ingredient in terms of micromoles per gram of non-absorbent substrate.

[9] The role of beneficial flora in the vaginal tract is mentioned in U.S. Patent No. 5,612,045 to Syverson, which is discussed elsewhere herein.

However, neither the Stolar nor D'Augustine, et al. references disclose applicants' claimed amounts of first active ingredient. For instance, while Stolar discloses the ratio of trimethoprim to sulfa drug to phenoxyethanol in the compositions disclosed therein, and the Examples of Stolar set forth the amount of phenoxyethanol in specific compositions, Stolar fails to disclose or suggest the amount of phenoxyethanol deposited on a non-absorbent substrate as set forth in applicants' claims. Additionally, while D'Augustine, et al. disclose the amount of drug that may be present in a formulation, and the amount of antibiotics that may be administered to a patient per day, D'Augustine, et al. fail to disclose or suggest the amount of antibiotics that may be deposited on a non-absorbent substrate, much less the amount of first active-ingredient as set forth in applicants' claims. Claims 7-9 are thus patentable for this additional reason.

Claims 14-25 are patentable under 35 U.S.C. §103(a) over Stolar (U.S. 4,470,978) in view of D'Augustine, et al. (U.S. 6,416,779) and Syverson (U.S. 5,612,045)

Claims 14-25 depend from claim 1 and further require the exoprotein inhibitor to comprise an effective amount of a second active ingredient having the general formula: R^{10}—O—R^{11}, wherein R^{10} is a straight or branched alkyl or straight or branched alkenyl having from 8 to about 18 carbon atoms and R^{11} is selected from the group consisting of an alcohol, a polyalkoxylated sulfate salt and a polyalkoxylated sulfosuccinate salt, and wherein the second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

Claim 1 is patentable over the combination of Stolar and D'Augustine, et al. for the reasons set forth above. Therefore, claims 14-25, which depend from claim 1, are patentable over the combination of Stolar and D'Augustine for the same reasons as claim 1 above. In particular, there is no reason for one skilled in the art to select phenoxyethanol alone, or a composition comprising phenoxyethanol, sulfa drugs, and trimethoprim, as disclosed in Stolar, to combine with the devices of D'Augustine, et al. for use in a vagina, in the absence of applicants' application as a blueprint.

The Syverson reference does not overcome this deficiency. Specifically, Syverson is merely directed to absorbent articles, such as catamenial tampons, which include an effective amount of an ether compound to substantially inhibit the production of exotoxins by Gram positive bacteria. Significantly, nowhere in Syverson is a first active ingredient as set forth in claim 1 even mentioned, much less that such a compound has antimicrobial properties or is effective in inhibiting the production of exoprotein from Gram positive bacteria.[10]

In the response to arguments section of the final Office action, the Examiner has stated that applicants' arguments are not persuasive because while the motivation to include the first claimed compound comes from the teachings of Stolar and D'Augustine, et al., D'Augustine, et al. and Syverson are in the same field of endeavor and thus the motivation to combine the compounds of Stolar and Syverson flows logically with an expectation to achieve the desired antibacterial and protein

[10] Syverson furthermore fails to disclose or suggest a non-absorbent substrate selected from the group consisting of a non-absorbent incontinence device, a

inhibiting effects.

In response, applicants again note that for the reasons set forth above, there is simply no motivation provided by any of the cited references to incorporate phenoxyethanol or the phenoxyethanol, sulfa drug, and trimethoprim containing compositions of Stolar into the vaginal devices of D'Augustine, et al. Whether or not D'Augustine, et al. and Syverson are in the same field of endeavor is irrelevant, as neither of these references provides any motivation or suggestion to incorporate phenoxyethanol or other compounds having the formula set forth in applicants' claim 1 into a non-absorbent substrate for insertion into a vagina. There is simply nothing in any of the cited references that would motivate one skilled in the art to incorporate a compound of the formula set forth in applicants' claim 1 in combination with an ether as set forth in claim 14 into a non-absorbent substrate for insertion into a vagina.

As such, claims 14-25 are patentable over the combination of Stolar, D'Augustine, et al., and Syverson.

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barrier birth control device, a tampon applicator, and a douche, but rather is directed solely to absorbent articles.

VIII. Conclusion

A prima facie case of obviousness has not been established pursuant to 35 U.S.C. § 103, because the cited art fails to disclose, teach and/or suggest all the elements of claims 1-4, 6-11, and 14-25. For this reason, and for those more fully stated above, Applicants respectfully request the Office's rejections be reversed and all pending claims be allowed.

The Commissioner is hereby authorized to charge $500 for the appeal brief and any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,

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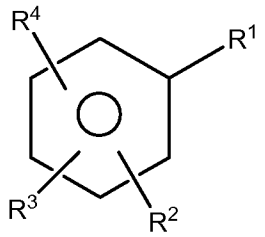
CMG/LJH/cms
By EFS

CLAIMS APPENDIX

1. (original) An exoprotein inhibitor for inhibiting the production of exoproteins from Gram positive bacteria in and around the vagina comprising a non-absorbent substrate for insertion into a vagina being selected from the group consisting of a non-absorbent incontinence device, a barrier birth control device, a tampon applicator, and a douche, the non-absorbent substrate having deposited thereon an effective amount of a first active ingredient having the general formula:



wherein R^1 is $-OR^6OH$; R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety; R^2, R^3, and R^4 are independently selected from the group consisting of H, OH, COOH, and $-C(O)R^9$; R^9 is hydrogen or a monovalent saturated or unsaturated aliphatic hydrocarbyl moiety, wherein the first active ingredient is effective in inhibiting the production of exoprotein from Gram positive bacteria.

2. (original) The exoprotein inhibitor as set forth in claim 1 wherein R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety having from 1 to about 15 carbon atoms.

3. (original) The exoprotein inhibitor as set forth in claim 2 wherein R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety having from 1 to about 10 carbon atoms.

4. (original) The exoprotein inhibitor as set forth in claim 2 wherein R^6 is a divalent saturated or unsaturated aliphatic hydrocarbyl moiety having from 1 to about 6 carbon atoms.

5. (withdrawn) The exoprotein inhibitor as set forth in claim 1 wherein R^2 is OH and R^3 is COOH.

6. (original) The exoprotein inhibitor as set forth in claim 1 wherein the first active ingredient is phenoxyethanol.

7. (original) The exoprotein inhibitor as set forth in claim 1 wherein the first active ingredient is present in an

amount of at least about 0.01 micromoles per gram of non-absorbent substrate.

8. (original) The exoprotein inhibitor as set forth in claim 1 wherein the first active ingredient is present in an amount from about 0.5 micromoles per gram of non-absorbent substrate to about 100 micromoles per gram of non-absorbent substrate.

9. (original) The exoprotein inhibitor as set forth in claim 1 wherein the first active ingredient is present in an amount from about 1.0 micromoles per gram of non-absorbent substrate to about 50 micromoles per gram of non-absorbent substrate.

10. (original) The exoprotein inhibitor as set forth in claim 1 further comprising a pharmaceutically active material selected from the group consisting of antimicrobials, antioxidants, anti-parasitic agents, antipruritics, astringents, local anaesthetics and anti-inflammatory agents.

11. (original) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second

active ingredient, said second active ingredient comprising a compound with an ether, ester, amide, glycosidic, or amine bond linking a C_8-C_{18} fatty acid to an aliphatic alcohol wherein the second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

12. (withdrawn) The exoprotein inhibitor as set forth in claim 11 wherein the C_8-C_{18} fatty acid is linked to a polyalkoxylated sulfate salt.

13. (withdrawn) The exoprotein inhibitor as set forth in claim 11 wherein the C_8-C_{18} fatty acid is linked to a sulfosuccinic salt.

14. (original) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient having the general formula:

$$R^{10}—O—R^{11}$$

wherein R^{10} is a straight or branched alkyl or straight or branched alkenyl having from 8 to about 18 carbon atoms and R^{11}

is selected from the group consisting of an alcohol, a polyalkoxylated sulfate salt and a polyalkoxylated sulfosuccinate salt wherein the second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

15. (original) The exoprotein inhibitor as set forth in claim 14 wherein R^{10} is a straight or branched alkyl group.

16. (original) The exoprotein inhibitor as set forth in claim 14 wherein R^{10} is a straight or branched alkenyl group.

17. (original) The exoprotein inhibitor as set forth in claim 14 wherein R^{10} is obtained from the group consisting of caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid and stearic acid.

18. (original) The exoprotein inhibitor as set forth in claim 14 wherein R^{11} is an aliphatic alcohol.

19. (original) The exoprotein inhibitor as set forth in claim 18 wherein R^{11} is an aliphatic alcohol selected from the

group consisting of glycerol, glycol, sucrose, glucose, sorbitol, and sorbitan.

20. (original) The exoprotein inhibitor as set forth in claim 19 wherein R^{11} is a glycol selected from the group consisting of ethylene glycol, propylene glycol, polypropylene glycol, and combinations thereof.

21. (original) The exoprotein inhibitor as set forth in claim 14 wherein the second active ingredient is selected from the group consisting of laureth-3, laureth-4, laureth-5, PPG-5 lauryl ether, 1-0-dodecyl-rac-glycerol, sodium laureth sulfate, potassium laureth sulfate, disodium laureth (3) sulfosuccinate, dipotassium laureth (3) sulfosuccinate and polyethylene oxide (2) sorbitol ether.

22. (original) The exoprotein inhibitor as set forth in claim 14 wherein the second active ingredient is present in an amount of at least about 0.0001 millimoles per gram of non-absorbent substrate.

23. (original) The exoprotein inhibitor as set forth in claim 14 wherein the second active ingredient is present in an

amount of at least about 0.005 millimoles per gram of non-absorbent substrate.

24. (original) The exoprotein inhibitor as set forth in claim 14 wherein the second active ingredient is present in an amount from about 0.005 millimoles per gram of non-absorbent substrate to about 0.2 millimoles per gram of non-absorbent substrate.

25. (original) The exoprotein inhibitor as set forth in claim 14 further comprising a pharmaceutically active material selected from the group consisting of antimicrobials, antioxidants, anti-parasitic agents, antipruritics, astringents, local anaesthetics and anti-inflammatory agents.

26. (withdrawn) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient, the second active ingredient comprising an alkyl polyglycoside effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

27. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the alkyl polyglycoside has an alkyl group having from about 8 to about 18 carbon atoms.

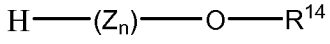
28. (original) The exoprotein inhibitor as set forth in claim 27 wherein the alkyl group is a linear alkyl group.

29. (withdrawn) The exoprotein inhibitor as set forth in claim 27 wherein the alkyl polyglycoside has an alkyl group having from about 8 to about 14 carbon atoms.

30. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the alkyl polyglycoside has an HLB of 12 to 14.

31. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the alkyl polyglycoside has an HLB of 10 to 15.

32. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the alkyl polyglycoside has the general formula:



wherein Z is a saccharide residue having 5 or 6 carbon atoms, n is a whole number from 1 to 6, and R^{14} is a linear alkyl group having from about 8 to about 18 carbon atoms.

33. (withdrawn) The exoprotein inhibitor as set forth in claim 32 wherein R^{14} is a linear alkyl group having from about 8 to about 14 carbon atoms.

34. (withdrawn) The exoprotein inhibitor as set forth in claim 32 wherein R^{14} is a linear alkyl group having from about 8 to about 12 carbon atoms.

35. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the second active ingredient is present in an amount of at least about 0.0001 millimoles per gram of non-absorbent substrate.

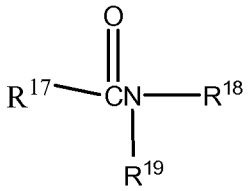
36. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the second active ingredient is present in an amount of at least about 0.005 millimoles per gram of non-absorbent substrate.

37. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the second active ingredient is present in an amount of at least about 0.005 millimoles per gram of non-absorbent substrate to about 2 millimoles per gram of non-absorbent substrate.

38. (withdrawn) The exoprotein inhibitor as set forth in claim 26 wherein the alkyl polyglycoside is selected from the group consisting of Glucopon 220, Glucopon 225, Glucopon 425, Glucopon 600, Glucopon 625, and TL 2141.

39. (withdrawn) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient selected from the group consisting of glycerol monolaurate and myreth-3-myristate wherein said active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

40. (withdrawn) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient having the general formula:



wherein R^{17}, inclusive of the carbonyl carbon, is an alkyl group having 8 to 18 carbon atoms, and R^{18} and R^{19} are independently selected from hydrogen or an alkyl group having from 1 to about 12 carbon atoms which may or may not be substituted with groups selected from ester groups, ether groups, amine groups, hydroxyl groups, carboxyl groups, carboxyl salts, sulfonate groups, sulfonate salts, and mixtures thereof wherein said second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

41. (withdrawn) The exoprotein inhibitor as set forth in claim 40 wherein R^{17} is derived from a saturated or unsaturated fatty acid.

42. (withdrawn) The exoprotein inhibitor as set forth in claim 41 wherein R^{17} is derived from an acid selected from the group consisting of caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, and stearic acid.

43. (withdrawn) The exoprotein inhibitor as set forth in claim 40 wherein the second active ingredient is selected from the group consisting of sodium lauryl sarcosinate, lauramide monoethanolamide, lauramide diethanolamide, lauramidopropyl dimethylamine, disodium lauramide monoethanolamide sulfosuccinate, and disodium lauroamphodiacetate.

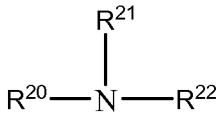
44. (withdrawn) The exoprotein inhibitor as set forth in claim 40 wherein the second active ingredient is present in an amount of at least about 0.0001 millimoles per gram of non-absorbent substrate.

45. (withdrawn) The exoprotein inhibitor as set forth in claim 40 wherein the second active ingredient is present in an amount of at least about 0.0005 millimoles per gram of non-absorbent substrate.

46. (withdrawn) The exoprotein inhibitor as set forth in claim 40 wherein the second active ingredient is present in an amount from about 0.005 millimoles per gram of non-absorbent substrate to about 0.2 millimoles per gram of non-absorbent substrate.

47. (withdrawn) The exoprotein inhibitor as set forth in claim 40 further comprising a pharmaceutically active material selected from the group consisting of antimicrobials, antioxidants, anti-parasitic agents, antipruritics, astringents, local anaesthetics and anti-inflammatory agents.

48. (withdrawn) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient having the general formula:



wherein R^{20} is an alkyl group having from about 8 to about 18 carbon atoms and R^{21} and R^{22} are independently selected from the group consisting of hydrogen and alkyl groups having from 1 to about 18 carbon atoms and which can have one or more substitutional moieties selected from the group consisting of hydroxyl, carboxyl, carboxyl salts and imidazoline wherein the second active ingredient is effective in substantially inhibiting the production of exoprotein from Gram positive bacteria.

49. (withdrawn) The exoprotein inhibitor article as set forth in claim 48 wherein R^{22} comprises a carboxyl salt, the

carboxyl salt having a cationic moiety selected from the group consisting of sodium, potassium and combinations thereof.

50. (withdrawn) The exoprotein inhibitor as set forth in claim 48 wherein R^{22} comprises an amine selected from the group consisting of lauramine, lauramino, propionic acid, sodium lauriminodipropionic acid, lauryl hydroxyethyl imidazoline and mixtures thereof.

51. (withdrawn) The exoprotein inhibitor as set forth in claim 48 wherein the second active ingredient is present in an amount of at least about 0.0001 millimoles per gram of non-absorbent substrate.

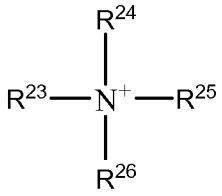
52. (withdrawn) The exoprotein inhibitor as set forth in claim 48 wherein the second active ingredient is present in an amount of at least about 0.005 millimoles per gram of non-absorbent substrate.

53. (withdrawn) The exoprotein inhibitor as set forth in claim 48 wherein the second active ingredient is present in an amount from about 0.005 millimoles per gram of non-absorbent

substrate to about 0.2 millimoles per gram of non-absorbent substrate.

54. (withdrawn) The exoprotein inhibitor as set forth in claim 48 further comprising a pharmaceutically active material selected from the group consisting of antimicrobials, antioxidants, anti-parasitic agents, antipruritics, astringents, local anaesthetics and anti-inflammatory agents.

55. (withdrawn) The exoprotein inhibitor as set forth in claim 1 further comprising an effective amount of a second active ingredient having the general formula:



wherein R^{23} is an alkyl group having from 8 to about 18 carbon atoms and R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of hydrogen and alkyl group having from 1 to about 18 carbon atoms and which can have one or more substitutional moieties selected from the group consisting of hydroxyl, carboxyl, carboxyl salts, and imidazoline wherein the second active ingredient is effective in substantially

inhibiting the production of exoprotein from Gram positive bacteria.

56. (withdrawn) The exoprotein inhibitor as set forth in claim 55 wherein the second active ingredient is triethanolamide laureth sulfate.

57. (withdrawn) The exoprotein inhibitor as set forth in claim 55 wherein the second active ingredient is present in an amount of at least about 0.0001 millimoles per gram of non-absorbent substrate.

58. (withdrawn) The exoprotein inhibitor as set forth in claim 55 wherein the second active ingredient is present in an amount of at least about 0.005 millimoles per gram of non-absorbent substrate.

59. (withdrawn) The exoprotein inhibitor as set forth in claim 55 wherein the second active ingredient is present in an amount from about 0.005 millimoles per gram of non-absorbent substrate to about 0.2 millimoles per gram of non-absorbent substrate.

60. (withdrawn) The exoprotein inhibitor as set forth in claim 55 further comprising a pharmaceutically active material selected from the group consisting of antimicrobials, antioxidants, anti-parasitic agents, antipruritics, astringents, local anaesthetics and anti-inflammatory agents.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.